REMARKS

The Final Office Action dated August 17, 2010, has been received and carefully noted. The above amendments and the following remarks are being submitted as a full and complete response thereto.

The foregoing amendment to the specification was made to insert the required paragraph incorporating the Sequence Listing filed concurrently herewith.

Claims 1 and 5-21 are pending in this application. Claims 1, 11, and 12 have been amended herein. Support for the amendments may be found in the specification as originally filed. Specifically, support for the amendment to SEQ ID NO: 1 can be found in the specification, for example, at page 6, line 24. Applicants submit that no new matter has been added. Applicants respectfully request reconsideration and withdrawal of the outstanding rejections.

Support for Sequence ID No. 1

The Office Action has taken the position that the amino acid sequence for SEQ ID NO: 1 recited in claims 1, 11, and 12 is not consistent with the disclosure of foreign priority application RM2004A000098 and the Sequence Listing submitted in parent international application PCT/IT2005/00088. Applicants have amended claims 1, 11, and 12 to recite that the amino acid sequence of SEQ ID NO: 1 is QFNWVSRLANLTQGEDQK. Also submitted herewith is a corrected Sequence Listing.

Rejections under 35 U.S.C. §102

Claim 11 is rejected under 35 U.S.C. §102(b) as allegedly anticipated by Fogelman et al. (WO 03/086326) and Wong et al. (*European Journal of Biochemistry*, 1994, Vol. 221, pages 917-925). Applicants respectfully traverse these rejections.

Applicants submit that claim 11 is directed to isolated immunogenic antigenic epitopes that are selected from the antigenic epitopes ***consisting of*** SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, or SEQ ID NO: 4. Fogelman et al. and Wong et al. merely disclose a larger sequence corresponding to human clusterin, and do not disclose or suggest isolated immunogenic antigenic epitopes. Specifically, none of the cited references disclose antigenic epitopes that ***consist of*** SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, or SEQ ID NO: 4.

Accordingly, claim 11 is not anticipated by Fogelman et al. or Wong et al. and applicants respectfully request that this rejection be withdrawn.

Claims 1, 5, 6, 11, and 15-21 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Yang et al. (PNAS, 2000, Vol. 97, pages 5907-5912, hereinafter "Yang"). The Examiner alleges that the polyclonal antiserum disclosed in Yang produced by immunizing rabbits with bacterially expressed human clusterin would inherently include the claimed oligoclonal antibodies. Applicants respectfully traverse this ground of rejection.

Yang discloses that polyclonal antisera directed against a bacterially-expressed nonglycosylated clusterin protein was generated in rabbits. With regard to the immunogen used, Yang discloses that the nuclear isoform of clusterin is obtained when protein translation starts from the second translation AUG site (page 5909, right column,

second last paragraph). Accordingly, Yang generated the nuclear isoform of clusterin by translating the clusterin protein from the second AUG start codon and used this full-length nuclear isoform to generate polyclonal antisera (page 5909, right column, last paragraph). In contrast, the claimed oligoclonal antibodies are generated using clusterin-specific short amino acid sequences comprising 10-20 amino acids (page 9, lines 20-23 of the specification). In other words, antigenic epitopes encountered by rabbit B cells in Yang are necessarily different from the antigenic epitopes encountered by rabbit B cells in the claimed invention.

Applicants further note that when a full length protein with a quaternary structure is used as an immunogen, different parts of the tertiary and quaternary structure of the protein are recognized by a large number of B cells and a polyclonal repertoire of antibodies directed against various epitopes of the tertiary and quaternary structure of the protein is generated. In contrast, when short amino acid sequences are used as immunogens, they are recognized by a restricted number of plasma B cells generating a repertoire of antibodies directed against the primary structure of the protein. Moreover, the repertoire of antibodies obtained using short amino acid sequences is similar to the monoclonal antibodies obtained with an immunization using hybridomas (page 8, lines 13-17 of the specification).

Thus, the polyclonal antibodies of Yang may not necessarily be directed against the same epitopes of clusterin as the claimed antibodies. Moreover, the overall sequence and structure of the antibodies generated in response to the full-length nuclear isoform of clusterin in Yang is likely to be different from the sequence and

structure of antibodies generated in response to the 10-20 amino acid sequences in the claimed invention.

The Examiner is respectfully reminded of MPEP § 2112(IV) which explains the requirements for an inherency rejection, in particular:

> "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. **The mere fact that a certain thing may result from a given set of circumstances is not sufficient**.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted) (emphasis added).

As noted above, the fact that a certain characteristic may be present in the prior art is not sufficient to establish the inherency. In fact, for at least the reasons discussed above, polyclonal antibodies of Yang are likely to be different from the claimed antibodies.

With regard to independent claim 11 directed to isolated antigenic epitopes, Yang fails to disclose antigenic epitopes that ***consist of*** SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, or SEQ ID NO: 4.

For at least the above reasons, applicants submit that claims 1 and 11 are not anticipated by Yang. Because claims 5, 6, and 15-21 depend from claim 1, these claims are also not anticipated by Yang. Accordingly, applicants respectfully request withdrawal of the anticipation rejection over Yang.

Rejections under 35 U.S.C. §103

Claims 1, 5, 11-18, 20, and 21 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over O'Sullivan et al. (*Cell Death and Differentiation*, 2003, Vol. 10, pages 914-927) in view of Wong et al., and Maloy and Coligan ('Selection of Immunogenic Peptides for Antisera Production,' in *Current Protocols in Immunology*, 1991, pages 9.3.1-9.3.5).

Claims 1, 5-8, 10-18, 20, and 21 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over O'Sullivan et al. in view of Wong et al., and Maloy and Coligan, as applied to claims 1, 5, 11-18, 20, and 21 above, and further in view of Kerr and Thorpe (*Immunochemistry LabFax*, 1994, pages ix-x, 118, 134-135, 142-143, 158-161).

Claims 1, 5, 6, 9-18, 20, and 21 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over O'Sullivan et al. in view of Wong et al., and Maloy and Coligan, as applied to claims 1, 5, 11-18, 20, and 21 above, and further in view of Scheele et al. (U.S. Patent No. 5,663,315).

Applicants respectfully traverse these rejections.

As set forth above with respect to the rejections under 35 U.S.C. § 102, Applicants submit that Wong et al. does not disclose sequences that ***consist of*** SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, and/or SEQ ID No. 4. Instead, Wong et al. merely discloses sequences surrounding the six glycosylation sites in human clusterin. Applicants submit that it would not be obvious to modify the disclosures of O'Sullivan et al., Wong et al., Maloy and Coligan, Kerr and Thorpe, and Scheele et al. to identify the presently-claimed immunogenic antigenic epitopes, or to raise antibodies against them.

Further, Applicants submit that the prior Declaration under 37 C.F.R. § 1.132 of Luigi G. Spagnoli demonstrated that the presently-claimed epitopes provide surprisingly strong sensitivity for detecting clusterin isoforms, and permit evaluation of clusterin increases in early stage cancer patients with higher sensitivity. In view of these unexpected results, Applicants submit that it would not have been obvious for one skilled in the art to modify the teachings of O'Sullivan, Wong et al., Maloy and Coligan, Kerr and Thorpe, and Scheele et al. in order to arrive at the presently-claimed invention.

For at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the obviousness rejections of claims 1, 5-8, 9-18, 20, and 21 over any combination of O'Sullivan, Wong et al., Maloy and Coligan, Kerr and Thorpe, and Scheele et al.

CONCLUSION

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event that this paper is not being timely filed, the Applicants respectfully petition for an appropriate extension of time. Any fees for such an extension, together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account Number 01-2300, referencing Docket Number 026073-00007.

Respectfully submitted,

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